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(58) Field of Search
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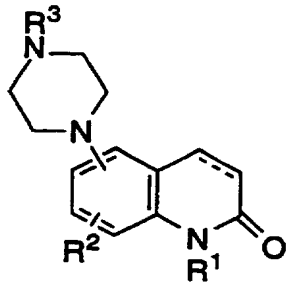
(54) Method of treating rheumatoid arthritis

(57) This invention relates to a method of treating arthritis comprising the administration to a patient in need of such treatment a non-toxic therapeutically effective amount of a piperazinyl carbostryl compound of Formula I



as disclosed in US 4,415,572.

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TITLE OF THE INVENTION

METHOD OF TREATING RHEUMATOID ARTHRITIS

BACKGROUND OF THE INVENTION

This invention relates to a method of treating rheumatoid arthritis comprising the administration to a patient in need of such treatment a non-toxic therapeutically effective amount of piperazinyl carbostryl compounds of Formula I, which compounds are disclosed in US 4,415,572 which is hereby incorporated by reference. In particular, this invention relates to the use of vesnarinone and related compounds in the treatment of rheumatoid arthritis. US 4,415,572 discloses the use of certain piperazinyl carbostryl compound, including vesnarinone, as a cardiotonic agent. More recently, vesnarinone has been reported to reduce the morbidity and mortality of pateints with chronic heart failure at a dose of 60 mg of active agent per day. See N. Engl. J. Med. 329(3):201-2 (1993).

Vesnarinone is unusual among modern medications in that it is an orally bioavailable drug which possesses a broad spectrum of biochemical activities and therefore an ill-defined mechanism of action. Vesnarinone has been shown to affect a number of cytokines including tumor necrosis factor-α (TNFα) as well as interferon (IFN)-λ, interleukin (IL)-1β and IL-2. See S. Sasayama, Pharmacology of Vesnarinone: Research findings on a potential cytokine inhibitor presented at Therapies for heart Disease: A glimpse into the future, ACC symposium, March 23, 1996 at Orlando Florida. See also Matsumori, A. et al, DAW 89(3) p 955-8 (March 1994).

Cytokines are known to be produced by a variety of cells, which are involved in immunoregulation and other physiological conditions, such as inflammation.

The term "cytokine" as used herein means any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines regardless of which cells produce them.

Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-2 (IL-2), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF-α) and Tumor Necrosis Factor-beta (TNF-β).

IL-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions. [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T-helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

There are many disease states in which IL-1 is implicated. Included among these diseases are rheumatoid arthritis, osteoarthritis, endotoxemia, toxic shock syndrome, other acute or chronic inflammatory diseases, such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic β cells.

Excessive or unregulated TNF production has been implicated in mediating or exacerbating rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

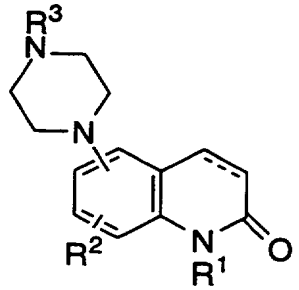
Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, *et al.*, Proc. Natl. Acad. Sci., 87:782-784 (1990)]. Therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T-cells. TNF has also been implicated in various roles with other viral infections, such as the cytomegalovirus (CMV), influenza virus and the herpes virus.

SUMMARY OF THE INVENTION

This invention relates to a method of treating rheumatoid arthritis disease comprising the administration to a patient in need of such treatment a non-toxic therapeutically effective amount of piperazinyl carbostryl compounds of Formula I, which compounds, which compounds are disclosed in US 4,415,572 which is hereby incorporated by reference. In particular, this invention relates to the use of vesnarinone and related compounds in the treatment of rheumatoid arthritis.

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses method of treating rheumatoid arthritis comprising the administration to a patient in need of such treatment a non-toxic therapeutically effective amount of a piperazinyl carbostryl compound of Formula I



wherein

R^1 represents a hydrogen atom, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, or a phenyl-lower alkyl group;

R^2 represents a hydrogen atom or a lower alkoxy group;

R^3 represents a hydrogen atom, a lower alkanoyl group, a furoyl group, pyridylcarbonyl group, a lower alkanesulfonyl group, a lower alkoxycarbonyl group, a lower alkoxycarbonyl-lower alkyl group, a phenylsulfonyl group which may be substituted with a lower alkyl group on the benzene ring thereof, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, a phenylcarbonyl group, a phenyl-lower alkyl group, or a phenyl-lower alkanoyl group, where each of said phenylcarbonyl group, phenyl-lower alkyl group and phenyl-lower alkanoyl group may be substituted with 1 to 3 of a lower alkoxy group, a halogen atom, a lower alkyl group, a cyano group, a nitro group, an amino group, a hydroxy group, a lower alkanoylamino group, a lower alkylthio group and a lower alkanoyloxy group, or with a lower alkylenedioxy group on the benzene ring thereof; and the bonding between the 3 and 4 positions of the carbostyril nucleus is a single bond or a double bond, and the pharmaceutically acceptable salts thereof.

The term "lower alkyl" as used herein refers to a straight or branched chain alkyl group having 1 to 6 carbon atoms such as a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, a tert-butyl group, a pentyl group, a hexyl group and the like.

The term "lower alkenyl" as used herein refers to a straight or branched chain alkenyl group having 2 to 6 carbon atoms, such as a vinyl group, an allyl group, a 2 -butenyl group, a 3 -butenyl group, a 1-methyallyl group, a 2-pentenyl group, a 2 -hexenyl group and the like.

The term "lower alkynyl" as used herein refers to a straight or branched chain alkynyl group having 2 to 6 carbon atoms such as an ethynyl group, a 2-propynyl group, a 2 -butynyl group, a 3 -butynyl group, a 1-methyl-2-propynyl group, a 2-pentynyl group, a 2-hexynyl group and the like.

The term "phenyl-lower alkyl" as used herein refers to a phenyl-lower alkyl group having a straight or branched chain alkyl group having 1 to 6 carbon atoms in the alkyl moiety such as a benzyl

group, a 2-phenylethyl group, a 1-phenylethyl group, a 3 -phenylpropyl group, a 4-phenylbutyl group, a 1,1-dimethyl-2-phenylethyl group, a 5-phenylpentyl group, a 6-phenylhexyl group, a 2-methyl-3-phenylpropyl group and the like.

The term "lower alkoxy" as used herein refers to a straight or branched chain alkoxy group having 1 to 6 carbon atoms such as a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, a tert-butoxy group, a pentyloxy group, a hexyloxy group and the like.

The term "lower alkanoyl" as used herein refers to a straight or branched chain alkanoyl group having 1 to 6 carbon atoms such as a formyl group, an acetyl group, a propionyl group, a butyryl group, an isobutyryl group, a pentanoyl group, a tert-butylcarbonyl group, a hexanoyl group and the like.

The term "halogen" as used herein refers to fluorine, chlorine, bromine and iodine.

The term "lower alkylenedioxy" as used herein refers to a straight or branched chain alkylenedioxy group having 1 to 4 carbon atoms such as a methylenedioxy group, an ethylenedioxy group, a trimethylenedioxy group and the like.

The term "lower alkanesulfonyl" as used herein refers to a straight or branched chain alkanesulfonyl group having 1 to 6 carbon atoms such as methanesulfonyl group, an ethanesulfonyl group, a propanesulfonyl group, an isopropanesulfonyl group, a butanesulfonyl group, a tert-butanesulfonyl group, a pentanesulfonyl group, a hexanesulfonyl group and the like.

The term "lower alkoxycarbonyl" as used herein refers to a straight or branched chain alkoxycarbonyl group having 1 to 6 carbon atoms in the alkoxy moiety such as a methoxycarbonyl group, an ethoxycarbonyl group, a propoxycarbonyl group, an isopropoxycarbonyl group, a butoxycarbonyl group, a tert-butoxycarbonyl group, a pentyloxycarbonyl group, a hexyloxycarbonyl group and the like.

The term "lower alkoxycarbonyl-lower alkyl" as used herein refers to a straight or branched chain lower alkoxycarbonyl-lower alkyl group having 1 to 6 carbon atoms in the alkoxy moiety and 1 to 6 carbon atoms in the alkyl moiety such as a methoxycarbonylmethyl group, a 3-methoxycarbonylpropyl group, a 4-ethoxycarbonylbutyl group, a 6-propoxycarbonylhexyl group, a 5-isopropoxycarbonylpentyl group, a 1,1-dimethyl-2-butoxycarbonylethyl group, a 2-methyl-3-tert-butoxycarbonylpropyl group, a 2-pentyloxcarbonylethyl group, a hexyloxycarbonylmethyl group and the like.

The term "phenylsulfonyl group which may be substituted with a lower alkyl group on the benzene ring" as used herein refers to phenylsulfonyl group which may be substituted with a straight or branched chain alkyl group having 1 to 6 carbon atoms on the benzene ring such as a phenylsulfonyl group, a p-toluenesulfonyl group, a 2-methylphenylsulfonyl group, a 3-ethylphenylsulfonyl group, a 4-propylphenylsulfonyl group, a 2-butylphenylsulfonyl group, a 3-tert-butylphenylsulfonyl group, a 4-pentylphenysulfonyl group, a 2-hexylphenylsulfonyl group and the like.

The term "phenylcarbonyl group substituted with 1 to 3 of a lower alkoxy group, a halogen atom, a lower alkyl group, a cyano group, a nitro group, an amino group, a hydroxy group, a lower alkanoylamino group, a lower alkylthio group and a lower alkanoyloxy group or with a lower alkylenedioxy group" refers to a phenylcarbonyl group substituted with 1 to 3 of a straight or branched chain alkoxy group having 1 to 6 carbon atoms, a halogen atom, a straight or branched chain alkyl group having 1 to 6 carbon atoms, a cyano group, a nitro group, an amino group, a hydroxy group, a straight or branched chain alkanoylamino group having 1 to 6 carbon atoms, a straight or branched chain alkylthio group having 1 to 6 carbon atoms and a straight or branched chain alkanoyloxy group having 1 to 6 carbon atoms, or with an alkylenedioxy group having 1 to 4 carbon atoms such as a 2-chlorobenzoyl group, a 3 -chlorobenzoyl group, a 4-chlorobenzoyl group, a 2-fluorobenzoyl group, a 3-fluorobenzoyl

group, a 4-fluorobenzoyl group, a 2-bromobenzoyl group, a 3-bromobenzoyl group, a 4-bromobenzoyl group, a 2-iodobenzoyl group, a 4-iodobenzoyl group, a 3,5-dichlorobenzoyl group, a 2,6-dichlorobenzoyl group, a 3,4-dichlorobenzoyl group, a 3,4-difluorobenzoyl group, a 3,5-dibromobenzoyl group, a 3,4,5-trichlorobenzoyl group, a 2-methylbenzoyl group, a 3-methylbenzoyl group, a 4-methylbenzoyl group, a 2-ethylbenzoyl group, a 3-ethylbenzoyl group, a 4-ethylbenzoyl group, a 3-isopropylbenzoyl group, a 4-hexylbenzoyl group, a 3,4-dimethylbenzoyl group, a 2,5-dimethylbenzoyl group, a 3,4,5-trimethylbenzoyl group, a 2-methoxybenzoyl group, a 3-methoxybenzoyl group, a 4-methoxybenzoyl group, a 2-ethoxybenzoyl group, a 3-ethoxybenzoyl group, a 4-ethoxybenzoyl group, a 4-isopropoxybenzoyl group, a 4-hexyloxybenzoyl group, a 3,4-dimethoxybenzoyl group, a 3,4-diethoxybenzoyl group, a 3,4,5-trimethoxybenzoyl group, a 2,5-dimethoxybenzoyl group, a 2-nitrobenzoyl group, a 3-nitrobenzoyl group, a 4-nitrobenzoyl group, a 2,4-dinitrobenzoyl group, a 2-aminobenzoyl group, a 3-aminobenzoyl group, a 4-aminobenzoyl group, a 2,4-diaminobenzoyl group, a 2-cyanobenzoyl group, a 3-cyanobenzoyl group, a 4-cyanobenzoyl group, a 2,4-dicyanobenzoyl group, a 3,4-methylenedioxybenzoyl group, a 3,4-ethylenedioxybenzoyl group, a 2,3-methylenedioxybenzoyl group, a 3-methyl-4-chlorobenzoyl group, a 2-chloro-6-methylbenzoyl group, a 2-methoxy-3-chlorobenzoyl group, a 2-hydroxybenzoyl group, a 3-hydroxybenzoyl group, a 4-hydroxybenzoyl group, a 3,4-dihydroxybenzoyl group, a 3,4,5-trihydroxybenzoyl group, a 2-formylaminobenzoyl group, a 3-acetylaminobenzoyl group, a 4-acetylaminobenzoyl group, a 2-acetylaminobenzoyl group, a 3-propionylaminobenzoyl group, a 4-butyrylaminobenzoyl group, a 2-isobutyrylaminobenzoyl group, a 3-pentanoylaminobenzoyl group, a 3-tert-butylcarbonylamino group, a 4-hexanoylaminobenzoyl group, a 2,6-diacetylaminobenzoyl group, a 2-methylthiobenzoyl group, a 3-methylthiobenzoyl group, a 4-methylthiobenzoyl group, a 2-ethylthiobenzoyl group, a 3-ethylthiobenzoyl group, a 3-isopropylthiobenzoyl group, a 4-

hexylthiobenzoyl group, a 3,4-dimethylthiobenzoyl group, a 2,5-dimethylthiobenzoyl group, a 3,4,5-trimethylthiobenzoyl group, a 2-formyloxybenzoyl group, a 3-acetyloxybenzoyl group, a 4-acetyloxybenzoyl group, a 2-acetyloxybenzoyl group, a 3-propionyloxybenzoyl group, a 4-butyryloxybenzoyl group, a 2-isobutyryloxybenzoyl group, a 3-pentanoyloxybenzoyl group, a 3-tert-butyryloxybenzoyl group, a 4-hexanoyloxybenzoyl group, a 3,4-diacetyloxybenzoyl group, a 3,4,5-triacetyloxybenzoyl group and the like.

The term "phenyl-lower alkyl group subsituted with 1 to 3 of a lower alkoxy group, a halogen atom, a lower alkyl group, a cyano group, a nitro group, an amino group, a hydroxy group, a lower alkanoylamino group, a lower alkylthio group and a lower alkanoyloxy group or with a lower alkylenedioxy group" refers to a phenyl-lower alkyl group subsituted with 1 to 3 of a straight or branched chain alkoxy group having 1 to 6 carbon atoms, a halogen atom, a straight or branched chain alkyl group having 1 to 6 carbon atoms, a cyano group, a nitro group, an amino group, a hydroxy group, a straight or branched chain alkanoylamino group having 1 to 6 carbon atoms, a straight or branched chain alkylthio group having 1 to 6 carbon atoms and a straight or branched chain alkanoyloxy group having 1 to 6 carbon atoms, or with an alkylenedioxy group having 1 to 4 carbon atoms such as a 2-chlorobenzyl group, a 2-(3-chlorophenyl)ethyl group, a 1-(4-chlorophenyl)ethyl group, a 3-(2-cluorophenyl)propyl group, a 4-(3-fluorophenyl)butyl group, a 1,1-dimethyl-2-(4-fluorophenyl)ethyl group, a 5-(2-bromophenyl)pentyl group, a 6-(3-bromophenyl)hexyl group, a 2-methyl-3-(4-bromophenyl)propyl group, a 3-iodobenzyl group, a 2-(4-iodophenyl)ethyl group, a 1-(3,5-dichlorophenyl)ethyl group, a 2-(3,4-dichlorophenyl)ethyl group, a 3-(2,6-dichlorophenyl)propyl group, a 4-(3,4-dichlorophenyl)butyl group, a 1,1-dimethyl-2-(3,4-difluorophenyl)ethyl group, a 5-(3,5-dibromophenyl)pentyl group, a 6-(3,4,5-trichlorophenyl)hexyl group, a 4-methylbenzyl group, a 2-(2-methylphenyl)ethyl group, a 1-(3-methylphenyl)ethyl group, a 3-(3-ethylphenyl)propyl group, a 4-(2-

ethylphenyl)butyl group, a 5-(4-ethylphenyl)pentyl group, a 6-(3-iospropylphenyl)hexyl group, a 2-methyl-3-(4-hexylphenyl)propyl group, a 2-(3,4-dimethylphenyl)ethyl group, a 2-(2,5-dimethylphenyl)ethyl group, a 2-(3,4,5-trimethylphenyl)ethyl group, a 4-methoxybenzyl group, a 3,4-dimethoxybenzyl group, a 3,4,5-trimethoxybenzyl group, a 1-(3-methoxyphenyl)ethyl group, a 2-(2-methoxyphenyl)ethyl group, a 3-(2-ethoxyphenyl)propyl group, a 4-(4-ethoxyphenyl)butyl group, a 5-(3-ethoxyphenyl)pentyl group, a 6-(4-isopropoxyphenyl)hexyl group, a 1,1-dimethyl-2-(4-hexyloxyphenyl)ethyl group, a 2-methyl-3-(3,4-dimethoxyphenyl)propyl group, a 2-(3,4-dimethoxyphenyl)ethyl group, a 2-(3,4-diethoxyphenyl)ethyl group, a 2-(3,4,5-trimethoxyphenyl)ethyl group, a 1-(2,5-dimethoxyphenyl)ethyl group, a 3-nitrobenzyl group, a 1-(2-nitrophenyl)ethyl group, a 2-(4-nitrophenyl)ethyl group, a 3-(2,4-dinitrophenyl)propyl group, a 4-(2-aminophenyl)butyl group, a 5-(3-aminophenyl)pentyl group, a 6-(4-aminophenyl)hexyl group, a 2,4-diaminobenzyl group, a 2-cyanobenzyl group, a 1,1-dimethyl-2-(3-cyanophenyl)ethyl group, a 2-methyl-3-(4-cyanophenyl)propyl group, a 2,4-dicyanobenzyl group, a 3,4-methylenedioxybenzyl group, a 3,4-ethylenedioxybenzyl group, a 2,3-methylenedioxybenzyl group, a 2-(3,4-methylenedioxyphenyl)ethyl group, a 1-(3,4-ethylenedioxyphenyl)ethyl group, a 3-methyl-4-chlorobenzyl group, a 2-chloro-6-methylbenzyl group, a 2-methoxy-3-chlorobenzyl group, a 2-hydroxybenzyl group, a 2-(3,4-dihydroxyphenyl)ethyl group, a 1-(3,4-dihydroxyphenyl)ethyl group, a 2-(3-hydroxyphenyl)ethyl group, a 3-(4-hydroxyphenyl)propyl group, a 6-(3,4-dihydroxyphenyl)hexyl group, a 3,4-dihydroxybenzyl group, a 3,4,5-trihydroxybenzyl group, a 2-formylaminobenzyl group, a 3-acetylaminobenzyl group, a 3-(2-acetylaminophenyl)propyl group, a 4-(4-acetylaminophenyl)butyl group, a 2-propionylaminobenzyl group, a 3-(3-butyrylaminophenyl)propyl group, a 4-(4-sobutyrylaminophenyl)butyl group, a 5-(2-tert-butylcarbonylaminophenyl)pentyl group, a

6-(3-pentanoylaminophenyl)hexyl group, a (2,4-diacetylamino)benzyl group, a 4-methylthiobenzyl group, a 2-(2-methylthiophenyl)ethyl group, a 1-(3-methylthiophenyl)ethyl group, a 3-(3-ethylthiophenyl)propyl group, a 4-(2-ethylthiophenyl)butyl group, a 5-(4-ethylthiophenyl)pentyl group, a 6-(3-isopropylthiophenyl)hexyl group, a 2-methyl-3-(4-hexylthiophenyl)propyl group, a 2-(3,4-dimethylthiophenyl)ethyl group, a 2-(2,5-dimethylthiophenyl)ethyl group, a 2-(3,4,5-trimethylthiophenyl)ethyl group, a 4-acetyloxybenzyl group, a 3,4-acetyloxybenzyl group, a 3,4,5-triacetyloxybenzyl group, a 1-(3-acetyloxyphenyl)ethyl group, a 2-(2-acetyloxyphenyl)ethyl group, a 3-(2-propionyloxyphenyl)propyl group, a 4-(4-pentanoyloxyphenyl)butyl group, a 5-(3-propionyloxyphenyl)pentyl group, a 6-(4-isobutyryloxyphenyl)hexyl group, a 1,1-dimethyl-2-(4-hexanoyloxyphenyl)ethyl group, a 4-butyryloxybenzyl group and the like.

The term "lower alkanoylamino" as used herein refers to a straight or branched chain alkanoylamino group having 1 to 6 carbon atoms such as a formylamino group, an acetylamino group, a propionylamino group, a butyrylamino group, an isobutyrylamino group, a pentanoylamino group, a tert-butylcarbonylamino group, a hexanoylamino group and the like.

The term "lower alkylthio" as used herein refers to a straight or branched chain alkylthio group having 1 to 6 carbon atoms such as methylthio group, an ethylthio group, a propylthio group, an isopropylthio group, a butylthio group, a tert-butylthio group, a pentylthio group, a hexylthio group and the like.

The term "lower alkanoyloxy" as used herein refers to a straight or branched chain alkanoyloxy group having 1 to 6 carbon atoms such as a formyloxy group, an acetyloxy group, a propionyloxy group, a butyryloxy group, an isobutyryloxy group, a pentanoyloxy group, a tert-butylcarbonyloxy group, a hexanoyloxy group and the like.

The term "phenyl-lower alkanoyl" as used herein refers to a phenylalkanoyl group having a straight or branched chain alkanoyl

group having 1 to 6 carbon atoms in the alkanoyl moiety such as a 2-phenylacetyl group, a 3-phenylpropionyl group, a 4-phenylbutyryl group, a 2-phenylbutyryl group, a 6-pehnylhexanoyl group, a 2-phenylpropionyl group, a 3-phenylbutyryl group, a 4-phenyl-3-methylbutyryl group, a 5-phenylpentanoyl group, a 2-methyl-3-phenylpropionyl group, and the like.

The term "phenyl-lower alkanoyl group substituted with 1 to 3 of a lower alkoxy group, a halogen atom, a lower alkyl group, a cyano group, a nitro group, an amino group, a hydroxy group, a lower alkanoylamino group, a lower alkylthio group and a lower alkanoyloxy group or with a lower alkylenedioxy group" refers to a phenyl-lower alkyl group substituted with 1 to 3 of a straight or branched chain alkoxy group having 1 to 6 carbon atoms, a halogen atom, a straight or branched chain alkyl group having 1 to 6 carbon atoms, a cyano group, a nitro group, an amino group, a hydroxy group, a straight or branched chain alkanoylamino group having 1 to 6 carbon atoms, a straight or branched chain alkylthio group having 1 to 6 carbon atoms and a straight or branched chain alkanoyloxy group having 1 to 6 carbon atoms, or with a straight or branched chain alkylenedioxy group having 1 to 4 carbon atoms such as a 2-(2-chlorophenyl)acetyl group, a 2-(3-chlorophenyl)acetyl group, a 2-(4-chlorophenyl)acetyl group, a 3-(2-fluorophenyl)propionyl group, a 4-(3-fluorophenyl)butyryl group, a 2-(4-fluorophenyl)acetyl group, a 5-(2-bromophenyl)pentanoyl group, a 6-(3-bromophenyl)hexanoyl group, a 2-methyl-3-(4-bromophenyl)propionyl group, a 2-(3-iodophenyl)acetyl group, a 2-(4-iodophenyl)acetyl group, a 2-(3,5-dichlorophenyl)acetyl group, a 2-(3,4-dichlorophenyl)acetyl group, a 3-(2,6-dichlorophenyl)propionyl group, a 4-(3,4-dichlorophenyl)butyryl group, a 2-(3,4-difluorophenyl)acetyl group, a 5-(3,5-dibromophenyl)pentanoyl group, a 6-(3,4,5- trichlorophenyl)hexanoyl group, a 2-(4-methylphenyl)acetyl group, a 2-(2-methylphenyl)acetyl group, a 2-(3-methylphenyl)acetyl group, a 3-(3-ethylphenyl)propionyl group, a 4-(2-ethylphenyl)butyryl group, a 5-(4-ethylphenyl)pentanoyl group, a 6-(3-isopropylphenyl)hexanoyl group, a 2-methyl-3-(4-

hexylphenyl)propionyl group, a 2-(3,4-dimethylphenyl)acetyl group, a 2-(2,5-dimethylphenyl)acetyl group, a 2-(3,4,5-trimethylphenyl)acetyl group, a 2-(4-methoxyphenyl)acetyl group, a 2-(3,4-dimethoxyphenyl)acetyl group, a 2-(3,4,5-trimethoxyphenyl)acetyl group, a 2-(3-methoxyphenyl)acetyl group, a 2-(2-methoxyphenyl)acetyl group, a 3-(2-ethoxyphenyl)propionyl group, a 4-(4-ethoxyphenyl)butyryl group, a 5-(3-ethoxyphenyl)pentanoyl group, a 6-(4-isopropoxyphenyl)hexanoyl group, a 2-(4-hexyloxyphenyl)acetyl group, a 2-methyl-3-(3,4-dimethoxyphenyl)propionyl group, a 2-(3,4-dimethoxyphenyl)acetyl group, a 2-(3,4-diethoxyphenyl)acetyl group, a 2-(3,4,5-trimethoxyphenyl)acetyl group, a 2-(2,5-dimethoxyphenyl)acetyl group, a 2-(3 -nitrophenyl)acetyl group, a 2-(2-nitrophenyl)acetyl group, a 2-(4-nitrophenyl)acetyl group, a 3-(2,4-dinitrophenyl)propionyl group, a 4-(2-aminophenyl)butyryl group, a 5-(3-aminophenyl)pentanoyl group, a 6-(4-aminophenyl)hexanoyl group, a 2-(2,4-diaminophenyl)acetyl group, a 2-(2-cyanophenyl)acetyl group, a 2-(3-cyanophenyl)acetyl group, a 2-methyl-3-(4-cyanophenyl)propionyl group, a 2-(2,4-dicyanophenyl)acetyl group, a 2-(3,4-methylenedioxyphenyl)acetyl group, a 2-(3,4-ethylenedioxyphenyl)acetyl group, a 2-(2,3-methylenedioxyphenyl)acetyl group, a 2-(3,4-methylenedioxyphenyl)acetyl group, a 2-(3,4-ethylenedioxyphenyl)acetyl group, a 2-(3-methyl-4-chlorophenyl)acetyl group, a 2-(2-chloro-6-methylphenyl)acetyl group, a 2-(2-methoxy-3-chlorophenyl)acetyl group, a 2-(2-hydroxyphenylacetyl group, a 2-(2,4-dihydroxyphenyl)acetyl group, a 2-(3-hydroxyphenyl)acetyl group, a 3-(4-hydroxyphenyl)propionyl group, a 6-(3,4-dihydroxyphenyl)hexanoyl group, a 2-(3,4-dihydroxyphenyl)acetyl group, a 2-(3,4,5-trihydroxyphenyl)acetyl group, a 2-(2-formylaminophenyl)acetyl group, a 2-(3-acetylaminophenyl)acetyl group, a 3-(2-acetylaminophenyl)propionyl group, a 4-(4-acetylaminophenyl)butyryl group, a 2-(2-propionylaminophenyl)acetyl group, a 3-(3-butyrylaminophenyl)propionyl group, a 4-(4-isobutyrylaminophenyl)butyryl group, a 5-(2-tert-

butylcarbonylaminophenyl)pentanoyl group, a 6-(3-pentanoylaminophenyl)hexanoyl group, a 2-(2,4-diacetylaminophenyl)acetyl group, a 2-(4-methylthiophenyl)acetyl group, a 2-(2-methylthiophenyl)acetyl group, a 2-(3-methylthiophenyl)acetyl group, a 3-(3-ethylthiophenyl)propionyl group, a 4-(2-ethylthiophenyl)butyryl group, a 5-(4-ethylthiophenyl)pentanoyl group, a 6-(3-isopropylthiophenyl)hexanoyl group, a 2-methyl-3-(4-hexylthiophenyl)propionyl group, a 2-(3,4-dimethylthiophenyl)acetyl group, a 2-(2,5-dimethylthiophenyl)acetyl group, a 2-(3,4,5-trimethoxyphenyl)acetyl group, a 2-(4-acetyloxyphenyl)acetyl group, a 2-(3,4-acetyloxyphenyl)acetyl group, a 2-(3,4,5-triacetyloxyphenyl)acetyl group, a 2-(3-acetyloxyphenyl)acetyl group, a 2-(2-acetyloxyphenyl)acetyl group, a 3-(2-propionyloxyphenyl)propionyl group, a 4-(4-pentanoyloxyphenyl)butyryl group, a 5-(3-propionyloxyphenyl)pentanoyl group, a 6-(4-isobutyryloxyphenyl)hexanoyl group, a 2-(4-hexanoyloxyphenyl)acetyl group, a 2-(4-butyryloxyphenyl)acetyl group, and the like.

As discussed above, vesnarinone is unusual among modern medications in that it possesses a broad spectrum of biochemical activities and therefore an ill-defined mechanism of action. Applicants believe that this broad spectrum of cytokine activity results in an rheumatoid arthritis therapy that is disease modifying, rather than merely symptom modifying. Thus, in one aspect applicants invention is directed to a method of reversing, halting or retarding rheumatoid arthritis comprising the administration of a compound of formula I, as described above.

In an alternative embodiment the invention encompasses a method of treating inflammatory Crohn's disease or inflammatory bowel disease comprising the administration to a patient in need of such treatment a non-toxic therapeutically effective amount of a piperazinyl carbostryl compound of Formula I as defined above. The pharmaceutical composition that may be used is the same or different from that described in this specification for rheumatoid arthritis.

This invention also concerns to pharmaceutical composition and methods of treatment of rheumatoid arthritis in a patient (including man and/or mammalian animals raised in the dairy, meat, or fur industries or as pets) in need of such treatment comprising administration of a piperazinyl carbostryl compound of Formula (I) as the active constituents.

The compounds of this invention represented by the Formula (I) can form pharmaceutically acceptable salts with acids and this invention also includes within its scope such pharmaceutically acceptable salts. The pharmaceutically acceptable acids which can be used for the salt formation can be various inorganic acids, for example, hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid, organic acids such as oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid and the like.

The compounds of the Formula (I) can be converted into a corresponding salt when they have an acid group by reacting the acid group with a pharmaceutically acceptable basic compound. Examples of basic compounds are inorganic basic compounds such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium hydrogencarbonate and the like.

The term "cytokine" as used herein means any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines regardless of which cells produce them. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-2 (IL-2), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF-α) and Tumor Necrosis Factor-beta (TNF-β).

By the term "cytokine interfering or cytokine suppressive amount" is mean an effective amount of a compound of Formula I which will, cause a decrease in the *in vivo* levels of the cytokine or its activity to normal or sub-normal levels, when given to the patient for the prophylaxis or therapeutic treatment of a disease state which is

exacerbated by, or caused by, excessive or unregulated cytokine production or activity.

For the treatment the above mentioned diseases, the compounds of Formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit Formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intracisternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl mono-stearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108;

4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan mono-oleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be Formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan mono-oleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be Formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such Formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be Formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of Formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of Formula (I) are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

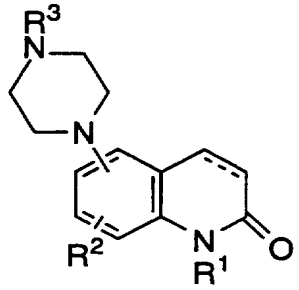
Dosage levels of the order of from about 2.5 mg to about 120 mg. per patient per day. For example, rheumatoid arthritis may be effectively treated by the administration of 15, 30, 60 or 90 mg per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a Formulation intended for the oral administration of humans may contain 15, 25, 30, 50, 60, 90, or 120 mg of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

WHAT IS CLAIMED IS:

1. A method of treating rheumatoid arthritis comprising the administration to a patient in need of such treatment a non-toxic therapeutically effective amount of a piperazinyl carbostryl compound of Formula I



wherein

R^1 represents a hydrogen atom, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, or a phenyl-lower alkyl group;

R^2 represents a hydrogen atom or a lower alkoxy group;

R^3 represents a hydrogen atom, a lower alkanoyl group, a furoyl group, a pyridylcarbonyl group, a lower alkanesulfonyl group, a lower alkoxycarbonyl group, a lower alkoxycarbonyl-lower alkyl group, a phenylsulfonyl group which may be substituted with a lower alkyl group on the benzene ring thereof, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, a phenylcarbonyl group, a phenyl-lower alkyl group, or a phenyl-lower alkanoyl group where each of said phenylcarbonyl group, phenyl-lower alkyl group and phenyl-lower alkanoyl group may be substituted with 1 to 3 of a lower alkoxy group, a halogen atom, a lower alkyl group, a cyano group, a nitro group, an amino group, a hydroxy group, a lower alkanoylamino group, a lower alkylthio group and a lower alkanoyloxy group, or with a lower alkylenedioxy group on the benzene ring thereof; and the bonding

between the 3- and 4-positions of the carbostyril nucleus is a single bond or a double bond; or its pharmaceutically acceptable salt.

2. A method according to Claim 1 comprising oral administration of a compound of Formula I.

3. A method according to Claim 1 wherein the disease is rheumatoid arthritis.

4. A method according to Claim 1 wherein

R^3 represents a phenylcarbonyl group which may be substituted with 1 to 3 of a lower alkoxy group, a halogen atom, a lower alkyl group, a cyano group, a nitro group, an amino group, a hydroxy group, a lower alkanoylamino group, a lower alkylthio group and a lower alkanoyloxy group or with a lower alkylenedioxy group on the benzene ring thereof.

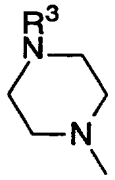
5. A method according to Claim 4 wherein R^1 and R^2 each represents a hydrogen atom.

6. A method according to Claim 4 wherein R^1 and R^2 each is other than a hydrogen atom.

7. A method according to Claim 5 wherein and 4-positions of the carbostyril nucleus is a single bond.

8. A method according to Claim 5 wherein and 4-positions of the carbostyril nucleus is a double bond.

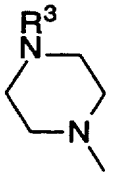
9. A method according to Claim 7 wherein the substituent of the Formula



is on the 5- or 6-position of the carbostyril nucleus.

10. A carbostyril compound or its pharmaceutically acceptable salt as claimed in claim 9 wherein R^3 represents a benzoyl group which is substituted with 1 to 3 of a lower alkoxy group and a halogen atom, or with a lower alkylenedioxy group on the benzene ring thereof.

11. A method according to Claim 8 wherein the substituent of the Formula



is on the 5- or 6-position of the carbostyril nucleus.

12. A carbostyril compound or its pharmaceutically acceptable salt as claimed in claim 11 wherein R^3 represents a benzoyl group which is substituted with 1 to 3 of a lower alkoxy group and a halogen atom, or with a lower alkylenedioxy group on the benzene ring thereof.

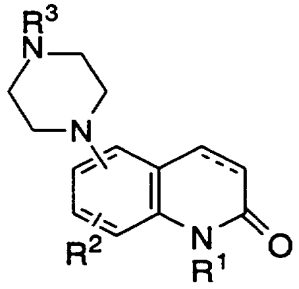
13. A method of Claim 1 wherein the compound of formula I is 6-[4-(3,4-Dimethoxybenzoyl)-1-piperazinyl]-3,4-dihydrocarbostyril.

14. A method of Claim 1 wherein the compound of formula I is 5-[4-(3,4-Dimethoxybenzoyl)-1-piperazinyl]-3,4-dihydrocarbostyril.

15. A method of Claim 1 wherein the compound of formula I is 6-[4-(4-Methoxybenzoyl)-1-piperazinyl]-3,4-dihydrocarbostyril.

16. A method of Claim 1 wherein the compound of formula I is 6-[4-(3,4-Dimethoxybenzoyl)-1-piperazinyl]-carbostyril.

17. A method of concurrently inhibiting TNF-α and IL-2 in a patient in need of such inhibition comprsing the administration of 30, or 60 mg per patient per day of a compound of Formula I



wherein

R^1 represents a hydrogen atom, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, or a phenyl-lower alkyl group;

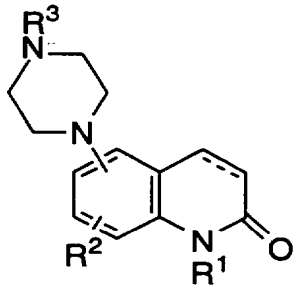
R^2 represents a hydrogen atom or a lower alkoxy group;

R^3 represents a hydrogen atom, a lower alkanoyl group, a furoyl group, a pyridylcarbonyl group, a lower alkanesulfonyl group, a lower alkoxycarbonyl group, a lower alkoxycarbonyl-lower alkyl group, a phenylsulfonyl group which may be substituted with a lower alkyl group on the benzene ring thereof, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, a phenylcarbonyl group, a phenyl-lower alkyl group, or a phenyl-lower alkanoyl group where each of said phenylcarbonyl group, phenyl-lower alkyl group and phenyl-lower

alkanoyl group may be substituted with 1 to 3 of a lower alkoxy group, a halogen atom, a lower alkyl group, a cyano group, a nitro group, an amino group, a hydroxy group, a lower alkanoylamino group, a lower alkylthio group and a lower alkanoyloxy group, or with a lower alkylenedioxy group on the benzene ring thereof; and the bonding between the 3- and 4-positions of the carbostyril nucleus is a single bond or a double bond; or its pharmaceutically acceptable salt.

18. A method according to Claim 2, 3, 13, 14,15 or 16 comprsing the oral administration of 30, or 60 mg per patient per day of a compound of Formula I.

19. A method of reversing, halting, or retarding rheumatoid arthritis in a patient in need of such reversing, halting, or retarding comprsing the administration of 30, or 60 mg per patient per day of a compound of Formula I.



wherein

R^1 represents a hydrogen atom, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, or a phenyl-lower alkyl group;

R^2 represents a hydrogen atom or a lower alkoxy group;

R^3 represents a hydrogen atom, a lower alkanoyl group, a furoyl group, a pyridylcarbonyl group, a lower alkanesulfonyl group, a lower alkoxycarbonyl group, a lower alkoxycarbonyl-lower alkyl group, a

phenylsulfonyl group which may be substituted with a lower alkyl group on the benzene ring thereof, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, a phenylcarbonyl group, a phenyl-lower alkyl group, or a phenyl-lower alkanoyl group where each of said phenylcarbonyl group, phenyl-lower alkyl group and phenyl-lower alkanoyl group may be substituted with 1 to 3 of a lower alkoxy group, a halogen atom, a lower alkyl group, a cyano group, a nitro group, an amino group, a hydroxy group, a lower alkanoylamino group, a lower alkylthio group and a lower alkanoyloxy group, or with a lower alkylenedioxy group on the benzene ring thereof; and the bonding between the 3- and 4-positions of the carbostyril nucleus is a single bond or a double bond; or its pharmaceutically acceptable salt.

The Patent Office

25

Application No:	GB 9708824.9	**Examiner:**	John Jenkins
Claims searched:	1-16, 18 & 19	**Date of search:**	14 July 1997

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): A5B (BHA,BJA)

Int Cl (Ed.6): A61K 31/495

Other: ONLINE: CAS-ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X	US 4415572	(TOMINAGA et al) See claims 14-17, 19, 21 & 22	10 & 12
X	EP 0638311 A1	(OTSUKA PHARMACEUTICAL) See page 4 lines 1-9, 25-40, 43-46, Example 3 & claim 3	1-19
P,A	Chemical Abstracts 126:181355 & JP 09002954 A2 (OTSUKA PHARMA) See abstract		
Y	Int. J. Immunopharmacol. 18(6/7), pages 371-378 (1996) (KAMBAYASHI et al)		1

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.